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THE USE OF ANTICOAGULANTS IN THE TREATMENT OF MYOCARDIAL INFARCTION

The possibility of preventing the extension of coronary thrombosis and the development of mural thrombi in the presence of myocardial infarction by the use of anticoagulants was suggested by Solandt, Nassim and Best[1,2] in 1938. These investigators had evolved a technique by which they were able to produce coronary thrombi and intracardiac mural thrombi in normal animals with regularity. Under identical experimental conditions, the development of such thrombi was prevented by heparinization. Their observations were not applied to man on any significant scale because of the difficulties and the risk felt to be inherent in the clinical use of heparin. In 1945 and 1946, Wright,[3] Nichol and Page,[4] and Peters, Guyther and Brambel[5] reported encouraging results following the use of the anticoagulant, dicumarol, in the treatment of coronary thrombosis with myocardial infarction in man. Accordingly, in the spring of 1946, the Board of Directors of the American Heart Association authorized the formation of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction.

Plan of the Study

One thousand thirty-one cases of coronary occlusion and myocardial infarction have been studied under the conditions of this investigation. Conventional methods of therapy alone were employed in slightly less than half of these cases. In the others anticoagulants were used in addition to conventional methods of treatment. 442 patients received conventional therapy and constituted "the control group". 589 patients received anticoagulants in addition to conventional therapy and constituted the "treated group".

The principles used in the administration of dicumarol and heparin during this study were as follows: (1) Heparin may be given for the first 48 hours or more if desired. (2) Prothrombin determinations are to be done each day and no dicumarol should ever be ordered unless the morning prothrombin report is available. (3) Dicumarol, 200 to 300 mg. daily, should be given until the prothrombin time is 30 seconds. (4) Dicumarol, 50 to 100 mg. daily, should be given if the prothrombin time is between 30 and 35 seconds. (5) Dicumarol should be withheld if the prothrombin time is 35 seconds or more; then, no drug is given until the prothrombin time is again down to 30 seconds or less, after which the drug is again given cautiously in doses of 100 mg. (6) The Link-Shapiro technique, using undiluted whole plasma, or the Quick method is to be used for determining the prothrombin clotting time, and it is suggested that the Link-Shapiro method, using 12.5 per cent diluted plasma, be employed as an additional check or safeguard. All prothrombin times are given in terms of the Link-Shapiro (undiluted) method. (7) Unless contraindications arise, dicumarol therapy is to be continued in the chosen cases over a minimal period of 30 days, preferably 30 days after the last thrombo-embolic episode. (8) In instances of hemorrhagic manifestations, the use of synthetic vitamin K preparations in doses of 60 to 75 mg. and transfusions of fresh whole blood (may be citrated) are recommended.

Composition of Sample

A comparison of the patients in the "control" group with those in the "treated" group showed a striking similarity in regard to age, history of previous infarction and estimated severity of the present attack. Although the estimate of severity of the attack for each patient at the time of diagnosis is admittedly arbitrary, the results suggested that the treated group contained a somewhat greater proportion of severely ill patients. The control and treated groups were closely similar when the medical histories of cardiovascular disease and the locations of the original infarcts were compared.

Of the patients in the control group who did receive some anticoagulant therapy, often for short periods only, 3 out of 5 were given anticoagulants after the development of a thrombo-embolic complication. The remaining patients received them because of pressure on the part of the family or a private physician or for miscellaneous reasons.

Correction of Rates

In the computation of the rates presented in the following paragraphs, certain corrections were made to simplify the presentation and to make sure that no bias existed which might favor the treated group. In both groups all rates for thrombo-embolic complications and hemorrhagic manifestations, as stated in this interim report, refer to conditions diagnosed by laboratory, electrocardiographic and clinical methods. Statistics based on findings at necropsy are not yet available but are being analyzed at this time.

Results of the Study

Whereas 23.4 per cent of the patients in the control group died, only 16 per cent of the patients in the treated group died. Thus, a third of the individuals who would have died without anticoagulant therapy survived the specific attack under consideration when anticoagulants were given. This difference is statistically significant. As previously anticipated, treatment with anticoagulants reduced the death rate largely by reducing the incidence of those thrombo-embolic complications which, directly or indirectly, result in death.

The death rates by week of illness were highest during the first two weeks, but were still considerable during the third and fourth week. For each period, the death rate for the control patients was found to be significantly greater than that for the

treated group. These figures indicate that anticoagulant therapy, if not used before, should be begun even as late as the second or third week after a myocardial infarction has occurred—or later, if complications have developed; and, secondly, that, to give maximal protection, anticoagulant treatment should be continued for at least four weeks after the last thrombo-embolic episode.

The greatest benefits in the reduction of mortality are in patients 60 years of age or older. Hemorrhagic complications have been so few and so mild throughout the entire study, and the benefits of treatment of patients in the older age group have been so pronounced, that we do not hesitate to prescribe anticoagulants for older patients. It should be recognized, however, that older patients have a higher incidence of unrelated complications. While the crude death rates for patients less than 60 in both the treated and the control groups did not show a significant difference, the incidence of thrombo-embolic complications was high in these groups, and the incidence of thrombo-embolic complications was markedly lower in the treated group. Such thrombo-embolic complications may not only be serious incidents in themselves, but they may result in such serious permanent disabilities as hemiplegia (following cerebral emboli), chronic venous insufficiency (following thrombophlebitis) or residual myocardial damage (following repeated myocardial infarction).

The number of thrombo-embolic complications per 100 cases recognized clinically was 41.8 in the control group and only 13.1 in the treated group. In other words, the patients in the treated group experienced less than one third as many thrombo-embolic complications as those in the control group did.

When the rates of thrombo-embolic complications by week of illness are considered, the advantage of using anticoagulants is clearly demonstrated for each of the first four weeks of illness. The incidence of thrombo-embolic complications, like that of deaths, is highest in the second week after coronary thrombosis or infarction, but is marked through the first four weeks. This, again, clearly indicates the importance of beginning anticoagulant therapy even as late as the second or third week after a myocardial infarction. Since it is impossible to predict from the condition of the patient during the first week whether thrombo-embolic complications will develop during subsequent weeks and whether death will occur from them, it is important to give anticoagulant therapy to all patients with coronary occlusion and myocardial infarction.

Conclusions

1. On the basis of data compiled from 1031 cases of coronary occlusion with myocardial infarction, it is concluded that the death rate and incidence of thrombo-embolic complications among patients treated with anticoagulants in addition to conventional methods is, during the first six weeks after an attack, markedly lower than among patients treated solely by conventional methods.

2. Anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication to such therapy exists.

3. In the absence of hemorrhagic conditions, the hazards from hemorrhage are not sufficient to contraindicate the use of anticoagulants in coronary occlusion, provided that there are facilities for adequate laboratory and clinical control.

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CASES SOLICITED FOR REGISTRY OF CARDIOVASCULAR PATHOLOGY

Contribution of cases is being currently solicited for the Registry of Cardiovascular Pathology which has been set up, under the Association's sponsorship, in the American Registry of Pathology at the Armed Forces Institute of Pathology in Washington, D. C. Wallace M. Yater, M.D., is Chairman of the Registry Committee and its other members are Jesse E. Edwards, M.D., Jane S. Robb, M.D., Joseph T. Roberts, M.D., and Helen B. Taussig, M.D. Communications regarding the registry should be addressed to The Director, Armed Forces Institute of Pathology, Washington 25, D. C.

The scope of the Registry is outlined as:

Congenital anomalies of the heart and larger blood vessels.

Subacute bacterial endocarditis.

The so-called "diseases of the Collagen System" including polyarteritis nodosa, temporal arteritis, disseminated lupus erythematosus, Libman-Sacks endocarditis, scleroderma, and amyloidosis of the heart.

Primary tumors of the heart, pericardium, blood vessels and lymphatics, including rhabdomyomatosis and glycogen-storage disease.

In addition, cases illustrating other diseases of the heart and larger blood vessels, in which consultation is desired or which are of especial interest because of rarity or noteworthy clinicopathologic correlation.

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